An Overview of Pulmonary Manifestations in Sickle Cell Disease

Eurasian Clinical and Analytical Medicine Review

Lungs in Sickle Cell Disease

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Abstract
The increased survival of patients with sickle cell disease (SCD) into adulthood leads an increased incidence of multiorgan dysfunction. The lung is one of the most common organs that may be involved in SCD. The pulmonary manifestations of SCD are the leading cause of morbidity and mortality in these patients. Although pulmonary manifestations of SCD are very common, they remain underdiagnosed by clinicians. The main pulmonary manifestations of SCD are acute chest syndrome, chronic dyspnea, asthma, sleep-disordered breathing, acute and chronic venous thromboembolic disease, pulmonary hypertension, and pulmonary fibrosis. Herein, the current knowledge of the pathophysiology, diagnosis, and treatment of pulmonary manifestations of SCD are reviewed.

Keywords
Sickle Cell Disease; Pulmonary Manifestation; Acute Chest Syndrome

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Introduction

Sickle cell disease (SCD) is one of the most common genetic disorders of hematological diseases (1). The prevalence of homozygous SS and heterozygous AS (sickle cell trait) genotypes is about 0.14% and 8.6%, respectively. There are more than 200 million carriers of sickle cell trait worldwide (1, 2). SCD encompasses a group of hemoglobinopathies characterized by amino acid substitutions in the beta globin chain. Hemoglobin S results from the substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain. Upon exposure to low oxygen tension the mutant haemoglobin S becomes less soluble and aggregates into large polymers (2, 3). This situation results in a distorted erythrocyte with marked decrease in its deformability contributing to the vaso-occlusive and haemolytic aspects of the disease. With improved supportive care the median age of survival has risen to about 48 years for women and about 42 years for men (3). As survival into adulthood has become more common in these patients, there has been an increased incidence of chronic organ invovements (2, 3).

The relationship between lungs and the various hematological disorders are identified in many clinical states. In addition to the opportunistic infections of lungs in immunocompromised patients, pulmonary entities including idiopathic hypereosinophilic syndrome, acute eosinophilic pneumonia, chronic eosinophilic pneumonia, bronchiolitis obliterans with organizing pneumonia are also in close relationship with hematological disorders (4, 5). It is well known that hematological changes may also be observed in chronic lung diseases with a complex cause-and-effect relationship (6). The pulmonary manifestation is the leading cause of morbidity and mortality in patients with SCD. Although pulmonary manifestations of SCD are very common, they remain underdiagnosed by clinicians. Herein, we review the pulmonary complications of SCD.

PULMONARY MANIFESTATIONS

The main pulmonary manifestations of SCD are:

- Acute chest syndrome
- Chronic dyspnea
- Asthma or recurrent wheezing without a diagnosis of asthma
- Sleep-disordered breathing
- Acute and chronic venous thromboembolic disease
- Pulmonary hypertension
- Pulmonary fibrosis

Acute Chest Syndrome: Acute chest syndrome, which is defined as an emerging radioopacity on chest X-ray accompanied by fever and/or emerging respiratory symptoms, is the most common form of acute pulmonary complication of SCD with a frequency of about 50% of patients (3, 4). Acute chest syndrome refers to a large spectrum of pulmonary diseases from a mild pneumonic illness to acute respiratory distress syndrome (7). Etiologies include pneumonia, pulmonary vasoocclusion and ischemia, fat embolization, thromboembolism and septic pulmonary embolism (8). These initial factors cause a decrease in alveolar oxygenation, which causes HbS polymerization. This event leads to a decrease in pulmonary blood flow that exacerbates vaso-occlusion, producing more severe hypoxia such that a vicious circle of hypoxia-HbS polymerization-vasoocclusion-altered pulmonary blood flow ensues (4, 7). The definition of acute chest syndrome encompasses cases where an infective microorganism is isolated and where no infective agent is identified. Although it is unique to SCD, in some cases acute chest syndrome may appear to be similar to bacterial pneumonia in a patient without SCD. On the other hand, infectious microorganisms were identified in 38% of cases who underwent detailed microbiological investigations (3, 7). While acute chest syndrome may have a severe hypoxia from mild hypoxia to respiratory failure and death, the presence of hypoxia is not included in the definition (2, 7).

Chronic Dyspnea: Chronic dyspnea is a common pulmonary symptom in SCD, particularly in adults. The etiology of chronic dyspnea in SCD is usually multi-factorial. Common causes of chronic dyspnea in SCD patients include anemia, asthma, deconditioning, venous thromboembolism, pulmonary hypertension and pulmonary fibrosis (3, 7). While chronic dyspnea may remain as a sole clinical antity in SCD, it may contribute to the other pulmonary complications of SCD.

Asthma: Asthma, which is a common antitiy in patients with SCD particularly in childhood, may affect the course of the disease (9). A number of studies suggest that asthma is a significant comorbidity in patients with SCD. Santoli and collegues measured pulmonary function in 49 patients with SCD and observed that 37% of the patients had obstructive lung disease. Twenty per cent of these patients had mixed obstructive and restrictive pulmonary function, and 20% had restrictive defects alone (3, 9, 10). On the other hand, the interrelationship of asthma and SCD is complex and stil not well-understood. Children with a history previous of acute chest syndrome are more likely to develop asthma (10). It is also thought that severe bronchospasm due to asthma may lead to local hypoxia and promote systemic inflammation and sickling (4, 10). Reversely, recurrent acute chest syndrome may lead to lung inflammation and therefore increased bronchial hyperreactivity (9). In another word, the cause-effcet relationship between asthme and SCD is stil sofisticated. Firstly, Perin et al provided the initial observation of a relationship between asthma and chest pain. In 1983, they described a 6-year old girl with SCD and severe asthma who was admitted to hospital for an asthma exacerbation and subsequently developed a chest pain episode (2, 7, 9). Since this original description, several studies have demonstrated and state the presence of this relationship (10). The largest study was based on the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective cohort of 291 infants with hemoglobin SS. Subjects were followed for a mean length of 11.0 years with a total follow-up of 4062 patient-years. 16.8% of the children had asthma and additinonalty these children had almost a two times greater rate of acute chest syndrome episodes when compared with children without asthma (11). On the other hand, the relationship between asthma and acute chest syndrome in adults with SCD has not been well documented. There are several points about the confusion of the relationship between asthma and SCD in adult patients. It is well known that asthma symptoms often improve in adulthood due to the incerase in airway size. Additionally, the incidence of acute chest syndrome is lower in adults; therefore, it is more difficult to asses a relationship between asthma and acute chest syndrome (9-11). Further studies are needed to clear this issue. Management of asthma in SCD should follow guidelines established for non-SCD patients with asthma.

Sleep Disordered Breathing: Sleep disordered breathing in SCD is most commonly associated to obstructive sleep apnea (OSA). OSA has been identified as an important comorbidity in SCD (12). As in other patients, OSA may contribute to chronic cardiopulmonary disease in SCD patients. Evaluation for OSA by polysomnography is needed in patients with complaints such as snoring, observed apneas during sleep non-restorative sleep, nocturnal gasping, or daytime hypersomnolence (12, 13). OSA also may lead to pulmonary hypertension in these patients. The treatment of OSA complicating SCD is essentially the same as that in children and adults without SCD (13).

Venous Thromboembolism and Pulmonary Thrombosis: SCD is a hypercoagulable state with reported abnormalities in coagulation and platelet functions. Pulmonary thromboembolism and microvascular occlusive thrombi are common in cases with SCD and may cause sudden death (14). A variety of mechanisms are postulated from low levels of protein S and C, to increased levels of factor VIII and tissue factor, and to en-

hanced platelet reactivity. The evaluation of acute venous thromboembolism (VTE) in SCD cases differs from the patients without SCD. The D-dimer and the modified Geneva score, the most common screening methods used for VTE, have limited value in SCD (14, 15). D-dimer levels are usually increased in SCD so that the increases in its levels are not meaningfull in terms of VTE (14). The poor predictive value of Geneva scoring is likely due to the overlap between the signs used in the scoring and the characteristics of acute chest syndrome of SCD (15). Therefore, computed tomography pulmonary angiogram is the most reliable diagnostic method for these patients. The treatment of acute VTE and pulmonary thrombosis in SCD is performed due to the classical guidelines for VTE. Additionaly, considering the increased risk of VTE in SCD cases, all hospitalised SCD patients with an acute medical illness should receive VTE prophylaxis (14, 15).

Pulmonary Hypertension: Pulmonary hypertension (PH) is increasingly recognized as a complication of SCD and also an independent risk factor for mortality in SCD (3). For example, the prevalence of pulmonary hypertension diagnosed by echocardiogram in patients examined at referral centers ranges from 20 to 30% (1, 16). In addition, various retrospective studies demonstrated that SCD cases with pulmonary hypertension have worse prognosis. One study demonstrated a 40% mortality rate in a 22-month follow-up period with an odds ratio of 7.86 and a 95% confidence interval of 2.63-23.4 (2, 16). The etiology of pulmonary hypertension in these patients seems to involve mechanisms that are common to both of these diseases. These processes include hemolysis, causing endothelial dysfunc¬tion and oxidative/inflammatory stress, chronic hypoxemia, chronic thromboembolism, chronic liver disease, asplenia and iron overload (17). Hemolytic anemia is an important process in the development of pulmonary hypertension in patients with hemoglob¬inopathies. Hemolysis results in the release of hemoglobin into plasma, where it reacts nitric oxide (NO) causing a state of resistance to NO-dependent vasodilatory effects (3,17). Other mechanisms that can contribute to pulmo¬nary hypertension in SCD cases are as follows: production of free radi¬cals, increased cellular expression of endothelin, platelet activation, and increased expression of endothelial adhesion mediating molecules (4, 18). Exertional dyspnea is generally the first symptom of PH in SCD patients. It is associated with impaired exercise tolerance, progressive heart failure, and a high mortality (16, 17). PH may be primarily diagnosed by non-invasive tests such as Doppler echocardiography, measurement of N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) levels and six minute walk test but definitive diagnosis requires right heart catheterization with demonstration of a resting mean pulmonary arterial pressure (PAP) ≥25 mmHg (2, 3, 17, 18). Although SCD patients with echocardiographic evidence of PH may not have the symptoms of cardiac failure, mortality is significantly increased in these patients who have PH (17). The mechanism of PH complicating SCD is unknown and likely to be multifactorial with possible causes including sickle cell related vasculopathy due to sequestration of sickle erythrocytes, chronic hypoxic stress causing irreversible remodelling of the vasculature with smooth muscle proliferation and fibrosis, increased blood viscosity with consequent right ventricular volume or pressure overload fat embolism, recurrent infection, recurrent pulmonary thromboembolism, and pulmonary scarring from repeated episodes of acute chest syndrom (1, 16, 18). Regardless of the underlying pathophysiology, the patients with PH are at risk for right sided heart failure (2, 17). Management of PH in SCD cases is similar to patients without SCD (17, 18).

Pulmonary Fibrosis: Pulmonary fibrosis usually occurs in patients with recurrent episodes of acute chest syndrome with pulmonary infarction. Sometimes PH may contribute to pulmonary fibrosis and this state was defined as 'sickle cell chronic lung disease (SCCLD)' previously (3, 19). Scattered areas of honeycombing in lung pharanchim in radiological imagings and restrictive pattern on pulmonary function tests are the typical findings of these patients (2, 3, 20). There is no specific treatment for pulmonary fibrosis in SCD, other than attention to measures to prevent future episodes of acute chest syndrome (19, 20).

Conclusion

Pulmonary complications are common causes of death in patients with SCD. The pulmonary manifestations of SCD are difficult to manage because they result from the complicated and complex pathophysiology of SCD. Considering that pulmonary manifestations are responsible for a big proportion of mortalities in SCD patients, clinicans should be aware of acute and chronic complications of SCD.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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